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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/913,467	12/11/2001	Walter Sebald	086033-000000US	2473

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EXAMINER
WOODWARD, CHERIE MICHELLE

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 06/29/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/913,467	SEBALD, WALTER	
	Examiner	Art Unit	
	Cherie M. Woodward	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 April 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23 and 25-28* is/are pending in the application.

4a) Of the above claim(s) *3 and 10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-2, 4-9, 11-23, and 25-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

1. Applicant's Amendment, filed 5 April 2006, is acknowledged. Claims 3 and 10 are withdrawn from examination as to a non-elected invention. Claims 1-2, 4-9, 11-23, and 25-28 are under examination. The text of those sections of Title 35, U.S. Code, not included in this action can be found in a prior office action.

Election/Restriction Requirement

2. Newly amended claims 3 and 10 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Claim 3 is drawn to SEQ ID NO: 3 or SEQ ID NO: 4, in the alternative. Claim 10 is drawn to SEQ ID NO: 5 or SEQ ID NO: 6 in the alternative. Applicants argue that claims 3 and 10 were improperly withdrawn from consideration in light of the Office Action of 29 September 2004, indicating that claims 3 and 10 were objected to, but otherwise allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. The restriction requirement, electing claims 1-26, as drawn to SEQ ID NO: 1, was made final in the Office Action of 29 September 2004 (see p. 2 of the Office Action, second full paragraph).

Claim 3 is drawn to SEQ ID NOs: 3 or 4, in the alternative. SEQ ID NO: 3 meets the limitations of the formula of SEQ ID NO: 1, but SEQ ID NO: 4 does not. SEQ ID NO: 4 contains a lysine residue in position 5 and a histidine residue in position 6. The formula of SEQ ID NO: 1 requires that no lysine, arginine, or histidine residue in positions 4-6 of the oligopeptide. As such, SEQ ID NO: 4 does not meet the structural requirements of the originally elected SEQ ID NO: 1. Claim 3 was withdrawn from consideration as being directed to a non-elected invention.

Claim 10 is drawn to SEQ ID NOs: 5 and 6 in the alternative. SEQ ID NO: 5 is a 120 amino acid polypeptide and SEQ ID NO: 6 is a 124 amino acid polypeptide. SEQ ID NOs: 5 and 6 were not previously elected SEQ ID Nos and they have not been searched by the examiner because they fall outside the scope of the six amino acid oligopeptide formula of SEQ ID NO: 1.

Moreover, because the restriction requirement was made final in the Office Action of 29 September 2004, Applicant's argument, filed 5 April 2006, traversing the finality of the restriction requirement, is excessively untimely.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 3 and 10 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claim Objections/Rejections Withdrawn

3. The rejections of claim 29 are moot in light of Applicant's cancellation of the claim.

4. The rejection of claims 1, 2, 4-9, 11-23, and 26-28 under 35 U.S.C. 112, first paragraph, as lacking enablement, are withdrawn in light of Applicant's amendments, filed 5 April 2006.

5. The rejection of claims 1, 2, 4-9, 11-23, and 25 under 35 U.S.C. 112, first paragraph, as lacking written description are withdrawn in light of Applicant's amendments, filed 5 April 2006.

Response to Arguments/Claim Rejections Maintained

Claim Rejections - 35 USC § 102

6. The rejection of claims 1, 2, 4-7, 9, and 11-23, and 25-27 under 35 U.S.C. 102(e) as being anticipated by U.S. Application publication number 2001/0020086 (now US Patent 6,960,452, issued 1 November 2005, priority to 27 August 1998) (the '086 application, previously cited in the Office Actions of 29 September 2004, 17 June 2005, and 5 January 2006) are maintained for the reasons of record and reasons set forth herein.

Applicant argues that the '086 application (now '452 patent) fails to anticipate amended claims 1 and 17 and claims dependent therefrom because the cited reference fails to teach every element of the currently claimed invention, as amended. Specifically, Applicant asserts that the '086 application ('452 patent) teaches the additions of heparin-binding domains to proteins that do not have a native heparin-binding domain because it uses the term "novel" in paragraph 11. Applicant also asserts that the '086 application ('452 patent) fails teach the addition of heparin-binding domains to polypeptides that naturally contain heparin-binding domains. Applicant's arguments have been fully considered, but they are not persuasive

The '086 application ('452 patent) teaches as previously cited in the Office Actions of 29 September 2004, 17 June 2005, and 5 January 2006, and herein. Additionally, the '086 application ('452

patent) teaches the addition and insertion of heparin-binding domains in growth factors that contain naturally occurring heparin-binding domains as well as in growth factors that do not contain naturally occurring heparin-binding domains (see, i.e. paragraph 0004 and corresponding column 1, lines 34-46). The '086 application ('452 patent) teaches the addition of heparin-binding domains to any growth factor (paragraph 0011; column 2, line 52). The phrase "any growth factor" encompasses the BMP and GDF proteins claimed by Applicant (paragraph 0014 of the '086 application and corresponding column 3, lines 27-55 of the '452 patent). The '086 application ('452 patent) teaches, "[f]usion proteins can be made of any growth factor for which the protein or DNA sequence is known, allowing the addition of novel domains such as heparin-binding domains or enzymatic substrates. These fusion proteins can be constructed so as to add a novel domain to either the N or C-terminus of the protein" ('086 application, paragraph 011; '452 patent, column 2, lines 51-57). As evidenced by the direct quote from the '086 application ('452 patent), the "novel domain" to be added refers to the new fusion protein domain that is to be added to either the N or C-terminus of the know sequence of the growth factor protein. There is no evidence in the '086 application ('452 patent) to suggest that the inventors were using the word "novel" to mean that heparin-binding domains were only being added to proteins that did not have naturally occurring heparin-binding sites. Further, Applicant's representative has provided no support for their apocryphal interpretation of the word "novel."

Claim Rejections - 35 USC § 103

7. The rejection of claims 1 and 8 under 35 U.S.C. 103 as being unpatentable over U.S. Application publication number 2001/0020086 (the '086 application (now US Patent 6,960,452, issued 1 November 2005, priority to 27 August 1998) in view of Linkhart *et al.*, (previously cited in the Office Actions of 29 September 2004, 17 June 2005, and 5 January 2006) is maintained for the reasons of record and the reasons set forth herein.

Applicant traverses the rejection stating that the examiner has misinterpreted the teaching of the '086 application as discussed in the response to the anticipation rejection. Applicant argues that there was no motivation to combine the teachings of the '086 application and the Linkhart *et al.*, reference. Applicant argues that the heparin-binding domains discussed in the '086 application would be expected to increase the binding of a polypeptide to heparin, but that there is no teaching in the '086 application that the heparin-binding domains confer binding to bone in a site-specific manner. Further, Applicant argues that that paragraph 0013 of the '086 reference merely explains that an excess of heparin-binding sites is essential to allow growth factors to bind to the matrix and that paragraph 0013 cannot be interpreted to

suggest or imply that additional heparin-binding sites should be introduced into growth factors. Applicant argues that biomaterials may well be equipped with additional heparin-binding sites, but that the situation in the '086 application does not apply to the instant claimed invention which relates to BMP or GDF polypeptide variants that have been designated to enhance the binding of these growth factors to heparinic sites of heparin-like molecules naturally occurring in the extracellular matrix. The Applicant argues that the '086 application only discloses the use of heparin-binding growth factors being non-covalently linked to a matrix or a gel. Further, the Applicant argues that the examiner's analysis can only be regarded as being taken from a hindsight perspective. Applicant's arguments have been considered, but they are not persuasive.

The '086 application ('452 patent) teaches as stated in the Office Actions of 29 September 2004, 17 June 2005, 5 January 2006, and *supra*. Contrary to the spurious arguments of Applicant's representative, the '086 application ('452 patent) teaches, "[f]usion proteins can be made of any growth factor for which the protein or DNA sequence is known, allowing the addition of novel domains such as heparin-binding domains or enzymatic substrates. These fusion proteins can be constructed so as to add a novel domain to either the N- or C-terminus of the protein" ('086 application, paragraph 011; '452 patent, column 2, lines 51-57). As evidenced by this direct quote, the '086 application ('452 patent) clearly and unambiguously teaches fusion proteins comprising any growth factor protein with the addition of heparin-binding domains to either the N- or C-terminal of the fusion protein. Applicant's argument that the disclosure neither suggests nor implies that additional heparin-binding sites should be introduced into a heparin-binding growth factor is without evidentiary support (see *supra*).

The Linkhart et al., reference teaches as stated in the Office Actions of 29 September 2004, 17 June 2005, 5 January 2006, and herein, that BMPs are related to transforming growth factor β (TGF-β) and that they are osteoinductive, and thus useful for bone healing (pp. 5S-6S). Linkhart et al. further teaches the need for matrices in order to use these BMPs (p. 5S). It would be obvious to one of ordinary skill in the art to combine the teachings of the '086 application ('452 patent) with those of Linkhart et al. to modify BMPs with heparin binding sites so that they could be used with matrices such as heparin and fibrin. One of ordinary skill would be motivated to do so because the '086 application patent teaches ways of modifying growth factors so that they may be attached to matrices, and Linkhart et al. teaches that such an attachment is useful for BMPs. Thus one of ordinary skill would expect improved healing from BMPs modified as taught by the '086 application ('452 patent). When the teachings of the '086 application are combined with the teachings of Linkhart *et al.*, it would be obvious to one of ordinary skill

in the art to use the heparin-binding sequestration techniques taught by the '086 application to target BMPs and GDFs to the site of bone, as taught by Linkhart *et al.*

In response to applicant's argument that the '086 application ('452 patent) only discloses the use of heparin-binding growth factors being non-covalently linked to a matrix or a gel, but not the use of heparin-binding growth factor fusion proteins in the absence of such matrices or gels, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). Moreover, Applicant's instant claim 26 is drawn to a matrix containing or coated with heparin or heparin-like substances and BMP or GDF polypeptide variants that are adsorbed to the heparin or heparin-like substances, like the one taught in the '086 application ('452 patent).

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

8. The rejection of claims 1, 2, 4-9, 11-23, and 25-28 under 35 U.S.C. 103 as being unpatentable over U.S. Application publication number 2001/0020086 (the '086 application; now US Patent 6,960,452, issued 1 November 2005, priority to 27 August 1998) (previously cited in the Office Actions of 29 September 2004, 17 June 2005, and 5 January 2006), in view of Ruppert *et al.*, Eur J. Biochem 1996 Apr 1; 237(1):295-302, (previously cited in the Office Action of 5 January 2006), have been fully considered but are not persuasive.

The '086 application ('452 patent) teaches as stated in the Office Actions of 29 September 2004, 17 June 2005, 5 January 2006, and *supra*. The '086 application ('452 patent) teaches adding heparin-binding domains to any growth factor to create a fusion protein or chimera. The '086 application ('452 patent) does not teach the process of producing a heparin-binding fusion protein polypeptide variant using CHO cells. Although the instant claims have been amended, the '086 application ('452 patent) teaches adding heparin-binding domains to any growth factor to create a fusion protein or chimera with increased heparin-binding activity. In further support, Ruppert et al., teach that "the occurrence of multiple basic triplets, i.e. three basic residues, is conspicuous in the heparin-binding sequences of BMP-2 (Fig. 8). The

significance of this motif is underscored by the observation that the X. laveis BMP-2 has the same N-terminal sequence with two conservative substitutions (K3/R3; K15/R15) only...Similar basic triplets albeit with a slightly different spacing exist in the N-termini of BMP-4 and the Drosophila dpp protein...Fragments of the motif are found in the longer N-terminal BMP-3,5,6,7 and 8 and also of human GDF-5...It can be envisions that the variations in the basic N-terminal sequences are reflected in the binding abilities of the individual proteins to heparin" (p. 300, first column, last paragraph, to second column, first paragraph).

For further clarification of the Office Action of 5 January 2006, Ruppert *et al.*, teach that the high unspecific binding of BMP-2 precludes a quantitative binding analysis with certain cells (p. 296, second paragraph) and proposes that this effect could be partially reduced after proteolytic cleavage of an N-terminal BMP-2 segments, as previously taught in the art (p. 296, second paragraph). Ruppert et al., teach that the highly basic N-terminal region of BMP-2 has a significant effect on increasing the specific activity of heparin-binding in a BMP-2 variant protein, as demonstrated by the peptide designated "peptide 1-17"(p. 298, column 2, first paragraph) and heparin-binding polypeptide variants produced in CHO cells (p. 297, column 2, first paragraph). "The positive effects of peptide 1-17 suggest that the heparin-binding site(s) of BMP-2 are located in the N-terminal basic sequence" (p. 298, second paragraph). Ruppert *et al.*, also demonstrate that the BMP-2/N-terminal IL-2 variant, designated EHBMP-2, "if compared with BMP-2, exhibited a 15-20 fold increased specific activity in the limb bud cell assay" (p. 298, column 2, last paragraph). Figure 6 shows the variant EHMBP-2 induced proteogylcan synthesis in embryonic chicken limb bud cells (p. 298, Figure 6). Ruppert *et al.*, explain that "[t]he high specific activity of this variant and its insensitivity to heparin and peptide 1-17 indicate that the two N-terminal sequence of dimeric BMP-2 normally limit its activity. Furthermore, these results strongly suggest that this modulation is due to heparin-binding sites interacting with proteoglycans on the limb bud cell surface and/or in the extracellular matrix" (p. 299, column 1, first paragraph). This is further explained by Ruppert et al., in that "[t]he 2-3 fold increase in the maximal BMP-2 response caused by heparin in the limb bud system was observed with both BMP-2 and the variant EHBMP-2, although the latter does not interact with heparin to a measurable extent. Thus, the potentiating effect of heparin cannot be mediated by BMP-2. One explanation for this puzzling observation could be that the BMP-2 response in these cells is normally limited by the activity of the receptor or another protein of the signal transduction pathway and that the activity of this limiting protein is increased in the presence of heparin" (p. 300, last paragraph to p. 301, first paragraph).

As stated in the previous Office Actions, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to make polypeptide variants with increased heparin-binding ability by following the teachings of the '086 application ('452 patent) and Ruppert et al., and produce them in CHO cells, as taught by Ruppert *et al.* One of ordinary skill in the art would have reasonably expected success because both the '086 application and Ruppert *et al.*, successfully produced heparin-binding growth factor fusion protein variants in *E. coli* and Ruppert *et al.*, successfully produced them in CHO cells. Both the '086 application ('452 patent) and Ruppert et al., teach the importance of triplets of basic residues to the N-termini of multiple BMPs and of GDF-5 (as taught by Ruppert et al.)

New Claim Rejections- Necessitated by Amendment

Claim Rejections - 35 USC § 112

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claim 7 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicant uses the phrase "essentially the same receptor binding affinity" in the amended claim, but fails to establish the metes and bounds of the phrase. "Essentially the same" receptor binding affinity could vary greatly or could mean no receptor binding affinity at all. It is noted that there are different binding affinities between T3, T4, and BMP-2 in Figure 4.

11. Claims 2, 4-9, 11-15, 17-23, and 25-28 are is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims recite the article "a". The proper article to use, when referring back to a polypeptide, a nucleic acid, or a host cell, for example, that has been claimed in a preceding claim, is "the." The use of the article "a" in dependent claims broadens the scope of potential polypeptides, for example, that may be read into a particular recitation of a claim. This rejection may be overcome by changing "a" to "the".

Conclusion

NO CLAIM IS ALLOWED.

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cherie M. Woodward whose telephone number is (571) 272-3329. The examiner can normally be reached on Monday - Thursday 9:00am-7:30pm (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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